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CURARE-LIKE ACTION OF POLY-METHYLENE *BIS*-QUATERNARY AMMONIUM SALTS

By Dr. W. D. M. PATON and Dr. E. J. ZAIMIS

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DURING a test of octamethylene-$\alpha\omega$-*bis*-trimethylammonium chloride for the power of liberating histamine, it was observed to be remarkably effective as a cause of neuromuscular block. Accordingly, a series of straight-chain aliphatic $\alpha\omega$-*bis*-trimethylammonium iodides have been synthesized from diamines by treatment in methyl alcoholic solution with methyl iodide and sodium hydroxide, and using the insolubility of these compounds in acetone, and the solubility of sodium iodide in this solvent for their isolation. All the compounds synthesized were tested for potency, and the octamethylene derivative (C_8) was the subject of more detailed pharmacological study.

In the rabbit head-drop test for curare-like activity, potency increased from the ethylene derivative to the octamethylene derivative, and the decamethylene derivative (C_{10}) was more potent still, 0·11 mgm./kgm. of the iodide being required to produce head-drop, compared with 0·25 mgm./kgm. of *d*-tubocurarine chloride. The potency in relation to *d*-tubocurarine chloride varied, however, with the test object; thus, the approximate ratio of an effective dose of the C_8 derivative to an equipotent dose of *d*-tubocurarine chloride was, on the cat's tibialis, $\frac{1}{3}$; on rabbit's head-drop, 3; on frog nerve-sartorius preparation, 3; on rat's diaphragm preparation, 50–100. In the cat's tibialis preparation[1], the C_8 derivative prevented the response of the muscle to stimulation of its motor nerve and to close arterial injection of acetylcholine, but not its response to direct stimulation. The conduction of impulses in nerve trunks was not affected by it.

While large doses of the C_8 derivative caused rapid neuromuscular block, moderate doses injected intravenously in the cat initially increased the response of tibialis to single maximal shocks applied to the motor nerve, and this response was followed by a small prolongation of the contraction, together with a widespread fibrillation of the musculature for 20–30 sec. not unlike that resulting from the injection of anticholinesterases. Intra-arterial injection of the C_8 derivative in a dose of 20 μgm. into the cat's

tibialis itself produced a twitch before block ensued. The curare-like action was not antagonized by prostigmine in doses adequate to antagonize the effect of *d*-tubocurarine chloride, either in the cat's tibialis or in the rabbit's head-drop test.

Comparison of potency with *d*-tubocurarine chloride was complicated by the remarkable finding that while *d*-tubocurarine chloride is unaltered in potency when given after these *bis*-quaternary salts, the converse is not true ; thus, following the injection of two-thirds head-drop dose, approximately twice as much of the C_{10} derivative was required to produce head-drop as was normally needed.

The results reported represent preliminary findings on a series of simple compounds, some of which have a potency which exceeds that of *d*-tubocurarine chloride. They serve to demonstrate, however, the importance of pharmacological testing of possible substitutes for *d*-tubocurarine chloride on more than one test object, and to suggest that before clinical application can be considered it is desirable to find some satisfactory antagonist to their effects.

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W. D. M. Paton
E. J. Zaimis
National Institute for Medical Research,
Hampstead, London, N.W.3.
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[1] Brown, G. L., *J. Physiol.*, **92**, 23 P (1938).

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